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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/839,649	04/19/2001	Alastair Murchie	22620/1222	2120

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PALMER & DODGE, LLP
KATHLEEN M. WILLIAMS / STR
111 HUNTINGTON AVENUE
BOSTON, MA 02199

EXAMINER
CHUNDURU, SURYAPRABHA

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,649	MURCHIE ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of Group I (claims 1-13, and 16) in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-13 and 16 are considered for examination in this office action. Claims 13-14 being non elected are withdrawn from further consideration.

3. The Information Disclosure Statement (Paper No. 10) filed on February 13, 2002 has been entered.

4. The disclosure is objected because of the following informalities:

(i) In Fig. 22 X and Y – axis are not labeled.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims recite '...sub-regions thereof' which make the claims unclear and indefinite because the phrase 'sub-regions thereof' is confusing for whether the ribosome fragment or sub-region of ribosome comprises other than the recited regions or do in fact comprise other regions of fragments or sub-regions derived from ribosome.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

a. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karn et al. (USPN. 6,316,194) and in view of Villsen et al. (J. Mol. Biol., 286: 365-374, 1999).

Karn et al. teach a method for determining a test compound binds to a target RNA, wherein Karn et al. disclose that the method comprises (i) incubating a test compound with target RNA and an antimicrobial molecule, measuring or detecting the change or modification of said target RNA and comparing the amount of change to that of a standard and identifying test compounds that bind to the target RNA (see column 3, lines 51-67, column 4, lines 1-26). Karn et al. also disclose that the method comprises (i) target RNA as ribosomal RNA or fragment or sub-regions of ribosome or complete RNA (see column 4, lines 36-42, column 5, lines 53-67, and column 6, lines 1-7); (ii) target RNA could be chemically modified RNA which enhances the stability of said target RNA (see column 4, lines 36-38, column 9, lines 2-66, column 10, lines 4-

67); test compounds could include peptides, peptiods, lipids, metal, nucleotides, nucleosides, small organic molecules, polyamines (see column 15, lines 62-67, and column 16, lines 1-11); test compounds may be derived from large libraries of synthetic or natural compounds (combinatorial library) (see column 16, lines 12-20); and the method is designed for a high-throughput screening format (see column 19, lines 30-46). Although Karn et al. teach the specific binding sites or regions of target RNA with various antibiotics, Karn et al. did not teach the RNA-modifying enzymes, which are involved in the underlying mechanism of action of these antibiotics.

Villsen et al. teaches the mechanism of action of antibiotic, erythromycin, wherein Villsen et al. teach that erythromycin acts via RNA-modifying enzyme, adenine-specific N-methyltransferse and alters or modifies ribosomal RNA (rRNA) target site and modification of rRNA by erythromycin methyltransferase confers resistance (see page 365, column 2, paragraph 1 and page 366, column 1 and 2). Further, Villsen et al. teach detection of target RNA modification by the incorporation of isotopic label s-sdenosyl-methionine using primer extension (see page 373, column 1, paragraphs 1-2, page 367, column 1, paragraph 1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of detecting a test compound as taught by Karn et al. with the RNA-modifying enzymes as taught by Villsen et al. which is well known in the art at the time the invention was made, because Karn et al. states that 'In most biological systems, the functions of RNA is often determined by the interactions between highly conserved RNA structures. In many instances it is desirable to develop drugs that bind RNA at sites of conserved structure to act as competitive inhibitors of the RNA function that is derived from various RNA

interactions. These types of drugs have potential applications in a wide range of diseases including bacterial, viral, and fungal infections. Many antibiotics function by inhibiting protein synthesis, and it has become increasingly clear that many do so by acting at the level of ribosomal RNA" (see column 1, lines 13-21 and column 2, lines 61-63). One such alternative mechanism of action of antibiotics expressly motivated by Villsen et al. is to provide "a better understanding of the three-dimensional structure of this RNA motif which will facilitate the design of small molecules of homologous shape that can be used to bind and inhibit the active site of the ErmE methyltransferase enzyme. This could lead to an effective means of combating MLS resistance" (see page 372, column 1, paragraph 2). An ordinary practitioner would have been motivated to combine the method of Karn et al. with the use of methyltransferases (RNA-modifying enzymes) as taught by Villsen et al., in order to achieve the expected advantage of developing a method for detecting a test compound that binds to target ribosomal RNA.

b. Claims 1-11 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stern et al. (USPN. 5,712,096) and in view of Villsen et al. (J. Mol. Biol., 286: 365-374, 1999).

Stern et al. teach a method for determining a test compound binds to a target RNA, wherein Stern et al. disclose that the method comprises (i) incubating a test compound with target RNA or an RNA analog molecule, and a ligand, measuring or detecting the disruption or modification of said target RNA binding complex and comparing the amount of change binding complex before and after addition of the test compound to the target RNA (see column 5, lines 13-25). Stern et al. also disclose that the method comprises (i) target RNA as ribosomal RNA or fragment or sub-regions of ribosome or complete RNA (see column 3, lines 21-58); (ii) target RNA could be chemically modified RNA which enhances the stability of said target RNA (see

column 2, lines 55-64, and column 3, lines 9-20); test compounds could include peptides, nucleotides, nucleosides, small organic molecules (see column 5, lines 1-12); the method includes probing reagent (suicide substrate or substrate that interacts with analog) (see column 5, lines 51-67, column 6, lines 1-24). Although Stern et al. teach the specific binding sites or regions of target RNA with various antibiotic analogs (see column10, lines 35-52, column 12, lines 54-67, and column 13, lines 1-6), Stern et al. did not teach the RNA-modifying enzymes, which are involved in the underlying mechanism of action of these antibiotics.

Villsen et al. teaches the mechanism of action of antibiotic, erythromycin, wherein Villsen et al. teach that erythromycin acts via RNA-modifying enzyme, adenine-specific N-methyltransferse and alters or modifies ribosomal RNA (rRNA) target site and modification of rRNA by erythromycin methyltransferase confers resistance (see page 365, column 2, paragraph 1 and page 366, column 1 and 2). Further, Villsen et al. teach detection of target RNA modification by the incorporation of isotopic label s-sdenosyl-methionine using primer extension (see page 373, column 1, paragraphs 1-2, page 367, column 1, paragraph 1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of detecting a test compound as taught by Stern et al. with the RNA-modifying enzymes as taught by Villsen et al. which is well known in the art at the time the invention was made, because Stern et al. states that 'most antibiotics that inhibit protein synthesis act directly on ribosomes. Several factors, all related to the structural complexity of ribosome, complicate screening assays that relay on binding of a potential drug candidate to a ribosomal target. Despite the complex structures and numerous associated proteins of complete ribosomes, we have discovered small oligoribonucleotide analogs that mimic small

domains of parental RNAs and that can fold and function autonomously for purposes of screening assays' (see column 1, lines 51-52, column 2, lines 12-31, and column 8, lines 38-42). One such potent antibiotic analog mechanism of action, expressly motivated by Villsen et al. is to provide "a better understanding of the three-dimensional structure of this RNA motif which will facilitate the design of small molecules of homologous shape that can be used to bind and inhibit the active site of the ErmE methyltransferase enzyme. This could lead to an effective means of combating MLS resistance" (see page 372, column 1, paragraph 2). An ordinary practitioner would have been motivated to combine the method of Stern et al. with the use of methyltransferases (RNA-modifying enzymes) as taught by Villsen et al., in order to achieve the expected advantage of developing a method for detecting a test compound that binds to target ribosomal RNA.

No claims are allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 703-305-1004. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
March 6, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER